Fluoroquinolones (and Quinolones)*

Overview

Quinolones or 4-quinolones, are synthetic carboxylic acid derivatives. Various alterations of the four quinolone ring structures have produced numerous broad-spectrum antimicrobial agents. Fluoroquinolone compounds became available for use in the mid-1980s. Fluoroquinolones were created by substitutions of a fluorine moiety at position 6. Although the non-fluorinated quinolones only feature a moderately extended Gram-negative spectrum, fluoroquinolones were developed for activity against both Gram-negative and Gram-positive organisms, chlamydiae and mycoplasmas. They are effective against some penicillin non-susceptible or multi-drug resistant pneumococci and some methicillin resistant *Staphylococcus aureus* (MRSA). The spectrum of activity against Gram-negative organisms includes activity against the Enterobacteriaciae, *M. catarrhalis*, β-lactamase producing *H. influenzae, Shigella, Salmonella* and *Neisseria* species. Several intracellular pathogens, for example *Brucella* species, are susceptible. In addition the fluoroquinolones are effective against *P. aeruginosa. Legionella pneumophila* and *Ureaplasma urealyticum* are atypical organisms that are susceptible as well.

The general category of quinolones is divided into quinolone classes: quinolone carboxylic acids, naphthydridine carboxylic acids, cinnoline carboxylic acids, pyridopyrimidine carboxylic acids and quinolizine carboxylic acids. The pharmacokinetic differences between classes and individual quinolones can be great.

Fluoroquinolones include enrofloxacin, norfloxacin, ciprofloxacin, orbifloxacin, ofloxacin, danofloxacin, flumequine, difloxacin and marbofloxacin. The mechanism of action of fluoroquinolones is interference with nucleic acid synthesis. The fluoroquinolones are bactericidal and target topoisomerase, or DNA gyrase, a substance that functions to preserve the state of supercoiling in replicating and non-replicating bacterial chromosomes. Anti-topoisomerase IV activity is the likely mechanism for activity against Gram-positive bacteria. Activity against DNA gyrase is the mechanism for effectiveness against Gram-negative bacteria, although newer fluoroquinolones may target both of these enzymes with equal affinity in any organism. In both cases the drug causes lethal breaks in DNA. Mammalian cells also feature topoisomerases, but those that function in mammalian cells fundamentally differ and are not affected by quinolones. Fluoroquinolones may exhibit a biphasic or post antibiotic effect against some bacteria, including *E coli* , *Klebsiella pneumoniae*, and *P aeruginosa*. This effect is thought to be related to suppression of RNA synthesis.

Nalidixic acid is considered the prototypical quinolone and is considered a first generation example of this class of antimicrobials. Nalidixic acid is a naphthydridine carboxylic acid. This drug was used for years in the treatment of urinary tract infections, but first generation quinolones are now considered obsolete. Enoxacin is an example of another naphthyridine carboxylic acid.

The quinolone carboxylic acid fluoroquinolones, ciprofloxacin and norfloxacin, are considered second generation fluoroquinolones and are primarily active against Gram-negative bacteria. Ciprofloxacin remains the most active quinolone against *P*

aeruginosa. Ofloxacin, a quinolizine carboxylic acid, is also considered a second generation quinolone.

Gatifloxacin, levofloxacin and moxifloxacin enjoy better activity against Gram-positive organisms, including penicillin resistant strains of *S pneumoniae*.

Use of β-lactams, aminoglycosides, clindamycin and metronidazole in combination with quinolones has resulted in synergism and increased efficacy in vitro. Nitrofurantoin used concurrently for urinary tract infections impairs the efficacy of quinolones. Quinolones also inhibit biotransformation of theophylline and can lead to toxic plasma levels of the drug.

Substitutions on the quinolone rings not only affect spectrum of activity but also affect chemical and physical properties. In general, the quinolones are absorbed well in the gut and penetrate tissues well, although the presence of antacids, dairy products, vitamins and citric acid reduce gastrointestinal absorption. High concentrations are found in the kidney, liver and bile, and notable concentrations are also found in bone, endometrium, prostatic fluid and cerebrospinal fluid (CSF), although CSF concentrations are insufficient for treatment of meningitis. Substitution of a piperazine ring at position 7 enhances tissue and bacterial penetration. The quinolones are generally poorly soluble in water between a pH of 6 and 8. In acid urine some quinolones form needle-shaped crystals. The urine of dogs and cats may be found to be acidic and thus, facilitate formation of these crystals. Renal excretion is the primary route of elimination for most quinolones, although biliary excretion is an important route of elimination with ciprofloxacin, pefloxacin and nalidixic acid. When using most quinolones in the presence of renal failure, dosages should be adjusted. Quinolones also appear often in high concentrations in the milk of lactating animals. These levels in milk may persist for long periods of time.

Oral or parenteral liquid formulations of quinolones usually contain soluble salts in stable aqueous solutions. Tablets, capsules and boluses are characterized by the presence of the active ingredient in betaine form (a neutral chemical compound comprised of a cationic functional group devoid of a hydrogen ion and an anionic functional group, the carboxylate group) or as a hydrochloride salt.

Adverse effects from use of fluoroquinolones include central nervous system manifestations, anaphylaxis, vasculitis, serum sickness like reactions, photosensitivity, tendinopathies, increased Q-T intervals and hypo or hyperglycemia. These adverse effects, although relatively common with older quinolones like nalidixic and oxolinic acids, are unusual with newer preparations. Administration of high doses of quinolones for lengths of time in pregnancy can result in embryo loss and maternal toxicity. These agents are not approved for use in children or immature animals due to associated arthropathies experienced in animal models. High doses administered over prolonged courses of therapy have resulted in cartilaginous erosions and resultant permanent lameness in growing dogs. There may be some indication that cartilaginous damage in weight bearing joints may be seen when these drugs are administered to horses, although extensive studies have not been performed examining this effect. However, it is estimated that approximately 150,000 prescriptions for ciprofloxacin are written each year in the

United States for children under 18 years of age, 20% of these prescriptions for children under one year of age. The American Academy of Pediatrics' Committee on Infectious Diseases has outlined several clinical conditions in which fluoroquinolones should be considered for therapy in pediatrics and, of course, judicious use is advised.

***References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**